REMARKS

Claims 15 through 27 are under examination in this application.

Amendment to the Specification

The amendment to paragraph [0001] was made to update status of applications that have granted or abandoned, and to correct a typographical error in the filing date of U.S. Patent 6,458,839.

Enclosed herewith is an updated application data sheet. Applicant(s) respectfully request an updated filing receipt with the above-noted corrections.

Rejection of Claims 15-27 Under 35 U.S.C. § 112, First Paragraph

Claims 15 through 27 were rejected under 35 U.S.C. § 112, first paragraph.

The present invention pertains to a method for treating columnar epithelial inflammation with a lipoxin A_4 compound.

The Office action asserts that "no evidence indicates that treatable disease was known to the applicant."

The term "columnar epithelium" is defined in the specification.

Paragraph number notations refer to Applicant's published patent application US 2004/0151712 A1.

> [0010] This invention pertains to methods for treating or preventing inflammation or an inflammatory response caused or contributed to by the perturbation of a columnar epithelium. The term "columnar epithelium" is intended to mean one or more of the epithelia of the intestine, kidney, stomach, liver, thyroid, trachea, lung, gall bladder, urinary bladder, bile ducts, pancreatic ducts, liver, and testicles. A columnar epithelium performs three functions. First, it acts as a physical barrier. Second, it moves fluids, electrolytes, and nutrients in vectors across the epithelium. Third, it synthesizes and releases bioactive molecules to influence other cell types.

The term "epithelial perturbation" is defined in the specification.

[0011] An epithelial perturbation is a deleterious alteration of one or more of the following: the normal barrier function; the transportation of fluids, electrolytes, or nutrients; or the synthesis or release of bioactive molecules by the epithelial cells. The term "epithelial perturbation" is meant to include one or more of the following events: abnormal fluid and electrolyte transport, especially chloride ion secretion, specific epithelial barrier dysfunction, and eventual mucosal breakdown. These perturbations lead to chronic and episodic inflammatory conditions.

The specification lists diseases of columnar epithelia.

[0016] Inflammatory Diseases of Columnar Epithelia

[0017] Epithelial perturbations cause or contribute to inflammatory intestinal disease states including: acute self-limited enterocolitis; viral infections such as non-specific enteritis or specific viral enteritis; ulcerative colitis; Crohn's disease; diverticulitis; bacterial enterocolitis, such as salmonellosis, shigellosis, campylobacter enterocolitis, or yersinia enterocolitis; protozoan infections such as amebiasis; helminthic infection; and pseudomembraneous colitis.

[0018] Additional inflammatory intestinal diseases are duodenitis resulting caused by infections, physical and chemical injuries, Celiac disease, allergic disease, immune disorders or stress ulcers; lymphocytic colitis; collagenous colitis; diversion-related colitis; acute self-limited colitis; microscopic colitis; solitary rectal ulcer syndrome; Behcet's disease; nonspecific ulcers of the colon; secondary ulcers of the colon; ischemic bowel disease; vasculitis; peptic duodenitis; peptic ulcer; bypass enteritis; ulcerative jejunoileitis; or nonspecific ulcers of the small intestine. Malabsorptive disorders include mucosal lesions associated with altered immune response such as idiopathic AIDS enteropathy, with viral or bacterial infections, or with miscellaneous diseases such as mastocytosis or eosinophilic gastroenteritis.

[0019] Perturbations of the epithelia of the lung and trachea cause or contribute to inflammatory lung diseases such as: cystic fibrosis, bronchiolitis, bronchitis, asthma, interstitial lung disease, eosinophilic pneumonias, tracheobronchitis, tracheoesophageal fistulas, and alveolitis.

[0020] Perturbations of the epithelium of the kidney cause or contribute to diseases such as: glomerulonephritis, nephritis, polycystic disease, ischemic disease, imrnune-complex-induced disease, immunopathogenic injuries, pyelonephritis, and tubulointerstitial disease.

[0021] Perturbations of the epithelium of the stomach cause or contribute to diseases such as gastritis and stomach ulcers.

[0022] This invention also encompasses inflammation of columnar epithelial caused or contributed to by surgery, allergy, chemical exposure, and physical injury.

The specification discusses methods of treating columnar epithelial inflammation

[0059] Methods of Treatment

[0060] This invention provides, in part, method of treating or preventing inflammation or an inflammatory response caused or contributed to by the activation of inflammatory cells which interact with a columnar epithelium. The interaction between activated inflammatory cells and the epithelium results in one or more epithelial perturbations. This anti-inflammatory treatment is the administration to a subject of an effective amount of a lipoxin, lipoxin analog, or combination thereof to inhibit the activation of the inflammatory cell such that the epithelial perturbation and inflammation or an inflammatory response are significantly reduced or eliminated.

[0061] A significant reduction of inflammation or an inflammatory response includes reducing or eliminating one or more of the symptoms associated with inflammation. For example, PMN transmigration stimulates electrogenic chloride secretion, which is the basis of secretory diarrhea, one of the symptoms of inflammatory bowel diseases. (Nash, S. et al. (1991). J. Clin. Invest 87: 1474-1477.) Additional nonlimiting examples of symptoms of inflammatory bowel diseases are cramping abdominal pain, malabsorption, dehydration, bloody stool, or fever. In addition to the inflammatory bowel disease listed above, bowel inflammation may also result from surgery, allergy, chemical exposure, or physical injury. Reduction of epithelial perturbation can also include inhibition of inflammatory cell activation. For example, a reduced perturbation can be the inhibition of PMN migration in the basal-to-apical direction represented by a decrease of at least about 25%.

[0062] Lipoxins include LXA_4 or LXB_4. The lipoxin analog can have a longer tissue half-life than the corresponding natural lipoxin. The lipoxin analog can also be lipophilic. The lipoxin analog can also be actively absorbed by the intestine. Lipoxins, lipoxin analogs, and combinations of lipoxins as used in these methods of treatment are defined above in the preceding two sections.

[0063] This invention also provides a method for the treatment or prevention of one or more of the symptoms of inflammatory diseases of columnar epithelia. In this method, the epithelial perturbations which cause or contribute to these symptoms may or may not be mediated by inflammatory cells. This method of treatment comprises the administration to a subject of an effective amount of a lipoxin, lipoxin analog, or combination thereof such that the epithelial inflammation or inflammatory response is significantly reduced or eliminated.

[0064] A significant reduction of inflammation or an inflammatory response includes reducing or eliminating one or more of the symptoms associated with inflammation. For example, abnormal chloride secretion causes or contributes to secretory diarrhea, a symptom of inflammatory bowel diseases. 5'AMP elicits chloride secretion from T84 intestinal epithelial cell monolayers, in a manner which may not always be dependent upon PMN. (Madara, J. L. et al. (1993) J. Clin. Invest 91:2320-2325.) Additional nonlimiting examples of symptoms of inflammatory bowel diseases are cramping abdominal pain, malabsorption, dehydration, bloody stool, or fever.

Example 4 of the specification discusses activity of lipoxin analogs on columnar epithelia.

Activity of Lipoxin Analogs on Columnar Epithelia

[0184] Several of the preferred lipoxin analogs (shown structurally as compounds 1 through 8 in Example 3) were prepared by total synthesis as described in Example 2. Following preparation and isolation of these compounds via HPLC, compounds were assessed to determine whether they retain biological activity using the epithelial cell transmigration assays as described above in Example 1.

[0185] Compounds 1 through 8 (10^{-7}-10^{-10}M) were found to inhibit neutrophil transmigration on epithelial cells. The acetylenic precursors (compound 1, 3, 5 and 7) were found to be physically more stable than their tetraene counterparts. Compound 7, which did not have an alcohol group in the C15 position or other modifications in the series, showed no biological activity in the assays. It would therefore appear that a substituent in the C15 position of lipoxin is necessary for the biological activity of at least lipoxin A_4 analogs. Lipoxin analogs 1 through 8 were found to block migration at potencies greater than or equal to synthetic lipoxin A_4. Compounds 1, 2 and 4 were found to be particularly effective. The results indicate that lipoxin A_4 analogs with modifications in C15-C20 positions retain their biological action and can inhibit PMN transmigration in columnar epithelia.

In summary, the specification provides a description that reasonably conveys to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed. The specification shows that treatable diseases were known to the Applicant and that the Applicant was in possession of the invention.

Reconsideration and withdrawal of this rejection is respectfully requested.

CONCLUSION

In light of the above, it is respectfully submitted that the present application is in condition for allowance. Reconsideration of the present application and a favorable response are respectfully requested. If a telephone conference would be helpful in resolving any remaining issues, please contact the undersigned at 612-340-8819.

No additional claim fees should be generated by this paper. However, the Commissioner is hereby authorized to charge any deficiencies or credit any overpayments to Deposit Account No. 04-1420.

Respectfully submitted,

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By: _____

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